

## **REMARKS**

Claims 1-51 were filed in the present case. The claims were subject to a restriction requirement. The Applicants elected Claims 1-43 in a prior response. As such, Claims 1-43 are pending and stand rejected by the Examiner. In the present Office Action, the Examiner made a number of arguments, objections, and rejections. For clarity, the rejections at issue are set forth by number in the order they are herein addressed:

- (1) Claims 1-6, 10-18, 22-31, and 35-43 stand rejected under 35 U.S.C. 102, as allegedly being anticipated by U.S. Patent 5,846,723 to Kim *et al.* (hereinafter the '723 patent); and
- (2) Claims 7-9, 19-21 and 32-34 stand rejected under 35 U.S.C. 103, as allegedly being obvious over the '723 patent.

### **I. The Claims are not Anticipated**

The Examiner has rejected Claims 1-6, 10-18, 22-31, and 35-43 under 35 U.S.C. 102, as allegedly being anticipated by the '723 patent (Office Action, pg. 2). The Applicants respectfully disagree and submit that the rejection is improper because the '723 patent does not teach all of the elements of Claims 1-6, 10-18, 22-31, and 35-43.

#### **A. Prior Arguments**

In order to facilitate rebuttal of the Examiner's present arguments, the Applicants have restated their prior arguments in response to the previous Office Action mailed 11/20/02.

The methods of the present invention involve identifying accessible sites on target sequences by analyzing the extension of a plurality of primers on the target (primers that bind to inaccessible sites are not extended, while primers that bind to accessible sites are extended). In an earlier office action response, the Applicants argued that, in contrast, the '723 patent specifically uses primers directed to accessible sites (*i.e.*, based on preexisting knowledge of the

accessible sites primers to inaccessible sites are avoided). For example, Col 1, line 60 of the '723 patent, in its broadest description of the technology, states that "polynucleotides that specifically hybridize to accessible regions are used."

In particular, in regard to independent Claim 1 (and dependent Claims 2-6 and 10-15), the '723 patent does not teach the step of "exposing said plurality of extension primers and said extension agent to said target nucleic acid under conditions wherein primers comprising first regions that are complementary only to an inaccessible site in said target nucleic acid are not extended by said extension agent, and wherein primers comprising first regions that are complementary to at least one accessible site of said target nucleic acid form an extension product." The Examiner cited Example 1 and Figure 1 of the '723 patent as teaching this element (previous Office Action, pg. 3). The Applicants respectfully disagree. Indeed, the '723 patent does not teach any method of selecting a primer that comprises **both** exposing the same target to a plurality of primers and forming **any** extension products. As such, the rejection of Claims 1-6 and 10-15 should be withdrawn.

With regard to independent Claim 16 and dependent Claims 17-18 and 22-27, the '723 patent does not teach the step of "determining at least a portion of the sequence of an extension products." The Examiner has pointed to no teaching in the '723 patent of this claim element. Nor does the '723 patent teach the step of "exposing said plurality of extension primers and said extension agent to said target nucleic acid under conditions wherein primers comprising first regions that are complementary only to an inaccessible site in said target nucleic acid are not extended by said extension agent, and wherein primers comprising first regions that are complementary to at least one accessible site of said target nucleic acid form an extension product." As such, the rejection of Claims 16, 17-18 and 22-27 should be withdrawn.

With regard to independent Claim 28 and dependent Claims 29-31 and 35-43, the cited reference does not teach the claim element of "exposing said plurality of extension primers and said extension agent to said target nucleic acid under conditions wherein primers comprising first

regions that are complementary only to an inaccessible site in said target nucleic acid are not extended by said extension agent, and wherein primers comprising first regions that are complementary to at least one accessible site of said target nucleic acid form an extension product." Further, the '723 patent does not teach the claim element of "treating said extension products with said amplification agent and said first and second amplification primers to generate one or more amplification products, said amplification products having a length, wherein said length of said amplification products provides a distance of an accessible site on said target nucleic acid from said first domain of said target nucleic acid" or the claim element of "determining a location of one or more accessible sites on said target nucleic acid using said distance." The Examiner cited Examples 1 and 2 and claims 26-29 and 34 of the '723 patent as teaching such elements (previous Office Action, pg. 6). However, the cited regions of the '723 patent (or any teaching in the '723 patent) do not teach Claim 28 of the present invention. The Examiner has pointed to no specific support for the Examiner's statement that the '723 patent teaches a method that comprises the step of generating amplification products where the length of the amplification products provides a distance of an accessible site from a first domain of a target nucleic acid. Nor has the Examiner pointed to any specific support in the '723 for the teaching of the claim element of determining a location of one or more accessible sites on said target nucleic acid using said distance. Rather, the '723 patent teaches away from such a method by utilizing primers that hybridize to known accessible regions of a target.

**B. Response to present Office Action**

In the present office action, the Examiner states "it is noted that the features upon which applicant relies (i.e., "identifying accessible sites on target sequences") are not recited at least in the rejected claims 1-6 and 10-15" (Office Action, pg. 8). The Applicants respectfully disagree. For Example, Claim 16 provides the method step of "d) identifying said accessible site by locating a region of said target nucleic acid adjacent to sequence that is complementary to said extension product." In addition, Claim 28 provides the step of "d) determining a location of one

or more accessible sites on said target nucleic acid using said distance." Thus, the Examiner's argument does not apply to Claims 16 and 28 and these claims should be passed to allowance. Regardless, the Applicants note that the argument is irrelevant as the Applicants have pointed to specific Claim steps in each of the rejected claims that are not taught by the '723 patent (see above and below).

In response to the Applicant's argument that the '723 patent does not teach the claim element of "exposing said plurality of extension primers and said extension agent to said target nucleic acid under conditions wherein primers comprising first regions that are complementary only to an inaccessible site in said target nucleic acid are not extended by said extension agent, and wherein primers comprising first regions that are complementary to at least one accessible site of said target nucleic acid form an extension product," the Examiner points to Column 13, line 49 to column 14, lines 23 as allegedly teaching this claim element. The Applicants respectfully disagree and submit that the cited portion of the '723 patent does not teach the portion of Claim 1 requiring that "primers comprising first regions that are complementary only to an **inaccessible** site in said target nucleic acid are not extended by said extension agent...." Rather, the cited portion of the '723 patent teaches that "To achieve linear amplification of both control and test polynucleotides in the same reaction..." (Column 13, lines 48-49). This is in contrast the cited portion of claim 1, which requires that primers directed towards inaccessible sites are not amplified.

In response to the Applicants argument that the '723 patent teaches away from the present invention (see above arguments), the Examiner states "it is noted that the features upon which applicant relies (i.e., "claimed invention is not based on the pre-existing knowledge of the accessible regions of a target") are not recited at least in the rejected claims 1-6 and 10-15." (Office Action, pg. 9). Applicants respectfully disagree with the Examiner's statement. With respect to Claims 16 and 28, as described above, the Applicants have pointed to portions of these claims that require such elements. With respect to Claim 1 (and dependent claims), the claims recite a set of primers whose design does not require that they bind to accessible sites. This is

clear from step b), which states that the primers provided in step a) may bind inaccessible sites. Thus, it is clear that the claimed primers are not designed to only bind to accessible sites as is taught in the '723. However, the Applicants submit that the Examiner's argument is irrelevant as, in response to every rejection by the Examiner, the Applicants have pointed to other specific claim steps not taught by the '723 patent. The '723 patent simply does not teach or suggest methods for identifying accessible sites by identifying extended primers from a set of primers that can bind to accessible and inaccessible sites.

The Examiner next states that "Secondly, all independent claims have the common element in section (a) "a target nucleic acid having at least one accessible site and at least one inaccessible site"." (Office Action, pg. 9). The Applicants submit that this argument is irrelevant as the remainder of the method steps of the independent claims clearly provide method steps not taught by the '723 patent (see above arguments).

The Examiner finally states "Third reasons is [sic] Kim et al clearly teaches, "Other accessible areas of hTR can be identified by similar assays." (Office Action, pg. 9). Again, this argument is not relevant to the present rejection as the '723 patent does not teach the methods of the **Applicant's presently claimed invention**.

In conclusion, the Applicants submit that the Examiner has failed to point to any teaching (as none exists) in the '723 patent that specifically teaches every step of the presently claimed invention. In particular, it appears that the Examiner has admitted that Claims 16 and 28 have elements not taught by the cited prior art. As such, the Applicants respectfully request that the rejection be withdrawn.

## **II. The Claims are Non-Obvious**

The Examiner has rejected Claims 7-9, 19-21 and 32-34 under 35 U.S.C. 103, as allegedly being obvious over the '723 patent (Office Action, pg. 6). The Applicants respectfully disagree. Applicants submit, in all cases, that the Examiner fails to provide a *prima facie* showing of obviousness as required under § 2143 of the Manual of Patent Examining Procedure

(MPEP). In particular, there are three elements that must be met to provide a prima facie obviousness showing. First, there must be a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings. Second, the prior art must provide a reasonable expectation of success should the suggested combination or modification take place. Finally, the prior art must teach or suggest all the claim limitations. A showing of obviousness will fail if any one of these elements is not met. Applicants submit that the Examiner has failed to meet any of the prima facie elements of obviousness.

#### **A. Prior Arguments**

In order to facilitate rebuttal of the Examiner's present arguments, the Applicants have restated their prior arguments in response to the previous Office Action mailed 11/20/02.

In particular, the Applicants submit that the cited reference does not teach or suggest all of the elements of the claimed invention as required for rejection under 35 U.S.C. 103. Claims 7-9 depend on independent Claim 1; Claims 19-21 depend on independent Claim 16; and Claims 32-34 depend on independent Claim 28. As described above, the '723 patent does not teach all of the elements of independent Claims 1, 16, and 28. In particular, the '723 patent does not teach the step of "exposing said plurality of extension primers and said extension agent to said target nucleic acid under conditions wherein primers comprising first regions that are complementary only to an inaccessible site in said target nucleic acid are not extended by said extension agent, and wherein primers comprising first regions that are complementary to at least one accessible site of said target nucleic acid form an extension product," the step of "determining at least a portion of the sequence of an extension product," or the steps of "treating said extension products with said amplification agent and said first and second amplification primers to generate one or more amplification products, said amplification products having a length, wherein said length of said amplification products provides a distance of an accessible site on said target nucleic acid from said first domain of said target nucleic acid" and "determining a location of one or more accessible sites on said target nucleic acid using said distance." Nor does the '723 patent suggest

modifying its teachings to provide these elements of Claims 7-9, 19-21 and 32-34. As such, the Examiner has failed to provide a *prima facie* case of obviousness. If an independent claim is nonobvious, any claim depending there from is nonobvious. MPEP 2143.03. As such, the applicants submit that Claims 7-9, 19-21 and 32-34 are non-obvious and respectfully request that the rejection be withdrawn.

**B. Response to present Office Action**

In response to the Applicant's argument that the '723 patent does not provide a motivation to combine or modify the reference to provide the presently claimed invention, the Examiner states "As clearly mentioned in the first office action that 103(a) rejection is not an obviousness rejection based on a secondary reference. It is an obviousness rejection based on "routine optimization". Therefore, no motivation is necessary to support the rejection." (Office Action, pg. 10). The Applicants respectfully disagree and submit that the Examiner is incorrect. The M.P.E.P clearly states that the lack of a secondary reference does not remove the burden on the Examiner to provide a motivation to modify the reference: "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." M.P.E.P. 2142. See also:

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. (M.P.E.P. 2143.01) "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55

USPQ2d 1313, 1317 (Fed. Cir. 2000). See also >*In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); < *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Thus, Applicants submit that the Examiner has failed to provide a motivation to modify the '723 patent to provide all of the elements of rejected Claims 7-9, 19-21 and 32-34. The Applicants further note that there is no legal standard for "routine optimization" as applied to rejections under U.S.C. 103. The standard is "modification" of the teachings of the prior art, not optimization (see e.g., above case law and M.P.E.P cites).

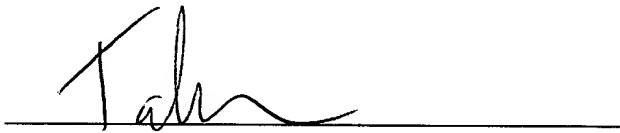
The Examiner next states "There is evidence in the Kim reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different target nucleic acid accessible sites were actually experimentally studied and found to be functional....(Office Action, pg. 11). The Applicants respectfully disagree and submit that the Examiner is mis-characterizing the '723 patent. As described above, the '723 patent does not teach or suggest the methods of the presently claimed invention, which require that "exposing said plurality of extension primers and said extension agent to said target nucleic acid under conditions wherein primers comprising first regions that are complementary only to an inaccessible site in said target nucleic acid are not extended by said extension agent, and wherein primers comprising first regions that are complementary to at least one accessible site of said target nucleic acid form an extension product," the step of "determining at least a portion of the sequence of an extension product," or the steps of "treating said extension products with said amplification agent and said first and second amplification primers to generate one or more amplification products, said amplification products having a length, wherein said length of said amplification products provides a distance of an accessible site on said target nucleic acid from said first domain of said target nucleic acid" and "determining a location of one or more accessible sites on said target nucleic acid using said distance." The Examiner has yet to point to

specific teachings of these method steps in the '723 patent. As such, the Applicants respectfully request that the rejection be withdrawn.

### **CONCLUSION**

For the reasons set forth above, it is respectfully submitted that Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: \_\_\_\_\_



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